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Differential effects of cocaine and ketamine on time estimation: Implications for neurobiological models of interval timing

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Abstract

The present experiment examined the effects of cocaine (0.0 and 15 mg/kg, i.p.) and ketamine (0.0, 10.0 and 15 mg/kg, i.p.) on timing behavior using a 12-s differential reinforcement of low rates (DRL) procedure and a 2- vs. 8-s bisection procedure in rats. DRL (time production) and bisection (time perception) procedures are sensitive to effects of dopaminergic drugs and provide an assessment of the accuracy and precision of interval timing as well as the subject's level of impulsivity. When administered to rats trained on either the DRL or the bisection procedure, cocaine shifted the psychophysical functions leftward relative to control conditions. In contrast, ketamine produced no change in the temporal control of behavior on either procedure. These differential effects of cocaine and ketamine are consistent with previous reports suggesting that dopamine levels in the dorsal striatum, but not in prefrontal cortex, ventral striatum or hippocampal regions, are crucial for the regulation of the speed of an internal clock.
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1. Introduction

Dissociative anesthetics, such as ketamine and phencyclidine, share many similarities with stimulant drugs, such as cocaine and methamphetamine, in terms of their effects on cognition and behavior. For example, both classes of drugs are known for their alterations of locomotor activity, pre-pulse inhibition, working memory and time perception—as well as for their abuse potential and ability to exacerbate psychosis in schizophrenic patients (e.g., Carlsson et al., 2001; Imre et al., 2006; Meck, 1996; Peoples et al., 1998; Rammsayer, 1999, 2006; Smith et al., 1998). As the release of dopamine (DA) is the primary neurochemical effect of cocaine and methamphetamine and a secondary effect of ketamine and phencyclidine, some of the behavioral effects of these agents may be related to a common dopaminergic mechanism. With regard to the neurochemical processes underlying this effect, there is evidence that glutamate modulation of striatal DA occurs both at the level of the dopaminergic cell bodies of the ventral tegmental area (VTA) and substantia nigra (SN) and the level of the glutamatergic afferents of the prefrontal cortex that modulate DA concentrations in the VTA, SN or in the striatum by providing excitatory input to the GABA interneurons (e.g., Monaghan and Cotman, 1985; Carter, 1982; Sesack and Pickel, 1992).

In terms of timing and time perception in the seconds-to-minutes range, it has been proposed that dopaminergic drugs modify the speed of clock-stage processes, whereas cholinergic drugs modify the speed of memory-stage processes (e.g., Buhusi, 2003; Buhusi and Meck, 2002, 2005; Hinton and Meck, 1996; Maricq and Church, 1983; Maricq et al., 1981; Meck, 1983, 1986, 1996; Meck and Church, 1987a,b). Indeed, these drugs can induce systematic changes in the temporal pattern of responding that are amenable to an information-processing framework of interval timing. For example, acute administration of methamphetamine, an indirect DA agonist, led to an immediate horizontal leftward shift in the temporal response function that was proportional in magnitude to the duration being timed (e.g., Matell et al., in press). Conversely, acute administration of haloperidol, a DA antagonist, led to an

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immediate horizontal rightward shift, again in a proportional manner (e.g., Lustig and Meck, 2005; MacDonald and Meck, in press). These proportional effects were explained by proposing that dopaminergic agonists increase the speed of the internal clock, such that the perceived time (i.e., the output of the clock stage) grows more rapidly than real time (e.g., Church, 1984; Church et al., 1991; Gibbon et al., 1984; Meck, 1983). For example, with a 15% increase in the speed of the clock, subjects will initiate responding 15% earlier, irrespective of the duration being timed. In contrast, an absolute shift in time estimation might result from drug-induced changes in attentional factors that could alter the latency to begin timing by a constant duration irrespective of the temporal criterion (e.g., Hinton and Meck, 1997; Penney et al., 1996).

DA-related drug effects have been characterized using several different interval-timing tasks (Paule et al., 1999). One example is the bisection procedure, which is classified as a time perception task (e.g., Church and Deluty, 1977; Maricq et al., 1981; Meck, 1983, 1986, 1991; Meck and Church, 1983; Meck et al., 1985). In the duration bisection procedure, a subject learns a correspondence between a "short" signal duration (e.g., 2-s noise) and a specific response (e.g., left lever press) and a correspondence between a "long" signal duration (e.g., 8-s noise) and an alternative response (e.g., right lever press). Typically, a pair of anchor durations (e.g., 2- and 8-s noise signals) is used during the first phase of training and reinforcement is contingent on a correct choice response. Following acquisition, unreinforced signals of intermediate durations are randomly intermixed with the anchor durations. The proportion of "long" responses is typically observed to increase as a function of signal duration, thus producing a sigmoidal-shaped curve. Moreover, the point of subjective equality (PSE—the signal duration that is classified as "long" on 50% of the trials) usually lies near the geometric mean of the anchor durations (e.g., Church and Deluty, 1977; Gibbon, 1981). Apropos to the current study, the entire psychophysical function (including the PSE) is shifted horizontally to the left during test sessions that immediately follow systemic injections of the DA-agonist methamphetamine, while injections of the DA-antagonist haloperidol shift the functions to the right in a similar manner. Both of these effects are proportional to the intervals being timed and as a consequence are consistent with a change in clock speed as opposed to a change in the latency to begin timing (e.g., Maricq and Church, 1983; Maricq et al., 1981; Meck, 1983, 1986, 1991, 1996; Meck and Church, 1983). In addition to the evaluation of drug effects on interval timing, the duration bisection procedure has also been used to study the modality differences in interval timing for auditory and visual stimuli (e.g., Lustig and Meck, 2001; Melgire et al., 2005; Penney et al., 2000, 2005).

Another behavioral task that is used to characterize interval-timing processes is the differential reinforcement of low rates (DRL) procedure. The DRL procedure is classified as a time production task that is used for evaluating interval timing as well as impulsivity/response inhibition (e.g., Jentsch and Taylor, 1999; Peterson et al., 2003; Richards et al., 1993). However, the extent to which DRL performance is mediated by impulsivity or timing, and whether the distinction between the two constructs is useful in the first place, is a matter of considerable debate. Indeed, there is evidence to support a role for impulsivity (e.g., Brookes et al., 1983; Ramirez et al., 1995; Sinden et al., 1986; Sokolowski and Salamone, 1994; Tonkiss et al., 1988) and timing (e.g., Liao and Cheng, 2005; McClure and McMillan, 1997; Niki and Watanabe, 1979; Sidman, 1955; Wiley and Willmore, 2000) in the DRL procedure.

During the typical DRL procedure, reinforcement is contingent on withholding a response for a minimum standard duration. Additionally, a response that is emitted before the standard duration expires is not reinforced and resets the experimental clock. In order to highlight the temporal regulation in the DRL procedure, the latency between successive responses (IRT—inter-response time) is quantified (see Richards and Seiden, 1991). Typically, the frequency distribution of the IRTs peaks slightly later than the trained standard duration (Richards et al., 1993). Moreover, dopaminergic drugs can be observed to shift the IRT distribution in a manner that parallels those observations made using other interval-timing tasks (e.g., Cheng and Liao, submitted for publication; Liao and Cheng, 2005; Popke et al., 2000a,b; Sabol et al., 1995).

The present series of experiments investigates the behavioral effects of cocaine and ketamine during rats' performance in duration bisection and DRL procedures. One goal is to characterize the degree to which the duration bisection and DRL procedures are functionally analogous (see MacDonald and Meck, 2004). Cocaine acts as an indirect DA agonist by binding to the dopamine transporter, which ultimately increases synaptic DA levels in both the dorsal and ventral striatum. Ketamine is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist that preferentially increases DA levels within the prefrontal cortex and limbic regions with relatively little, if any, effect on dorsal striatal DA levels (e.g., French, 1994; McGeer et al., 1977; Moghaddam et al., 1990; Verma and Moghaddam, 1996). Given the relationship between dorsal striatal DA levels and clock speed, we expect that cocaine will provide evidence of an increase in clock speed by shifting the PSE of the duration bisection function leftward. However, ketamine is not expected to have a similar effect on the PSE because it does not increase dorsal striatal DA levels sufficiently enough to affect clock speed. To the extent that temporal perception and production share the same timing system, a specific drug (e.g., cocaine or ketamine) would be expected to produce similar effects on DRL and bisection performance. In contrast, differential effects of the same drug on perception and production tasks would be expected to occur to the extent that the two tasks are influenced to a greater or lesser extent by different behavioral processes (e.g., timing vs. impulsivity—see Van Den Broek et al., 1987, 1992 or signal modality—see Lustig and Meck, 2001; Meck and Church, 1982; Penney et al., 2000) or different brain mechanisms (e.g., Hazeltine et al., 1997; Ivry and Hazeltine, 1995).

2. Materials and methods

2.1. Subjects

The subjects were 16 Sprague–Dawley male rats approximately 4 months of age at the beginning of the experiment. Six rats served

in the DRL procedure and 10 rats served in the bisection procedure as described below. Rats were housed in pairs in a temperature-controlled room, under a 12-h light/12-h dark cycle. Rats were provided free access to water in their home cages and were maintained at 85% of their 4 months *ad lib* weights by restricting access to food (Rodent Diet 5001, PMI Nutrition International, Inc., Brentwood, MO). Experiments were conducted in accordance with standard procedures approved by the Institutional Animal Care and Use Committee of Duke University.

2.2. Apparatus

The apparatus consisted of 10 standard lever boxes (MED Associates, Inc., Model ENV-007) housed in light and sound attenuating cubicles (MED Associates, Inc., Model ENV-019). Each lever box had inside dimensions of approximately 24 cm × 31 cm × 31 cm. The top, side walls and door were constructed of clear acrylic plastic. The front and back walls were constructed of stainless steel, and the floor was comprised of 19 parallel stainless steel bars. Each lever box was equipped with two response levers (MED Associates, Inc., Model ENV-112) situated on the front wall of the lever box. Noyes 45-mg precision food pellets (Research Diets, Inc., New Brunswick, NJ) could be delivered by a pellet dispenser (MED Associates, Inc., Model ENV-203) to a food cup on the front wall, 1 cm above the floor. A 28-V, 80-mA, 2500-lx house light was mounted at the center-top of the front wall and could be used to illuminate the box. The brightness of the light stimulus was measured with a light meter (Lutron Electronics Co., Cooperburg, PA, Model LX-102), positioned in the center of the lever box. An 80-dB auditory stimulus could be presented using a white-noise amplifier/speaker system (MED Associates, Inc., Model ENV-225) mounted on the opposite wall from the levers. A 60-dB sound produced by a ventilation fan was present throughout all procedures. The intensity of the white noise stimulus, as well as the intensity of the fan, was measured with a sound level meter (Realistic Radio Shack, Model 33-2050) from the center of the box.

2.3. Magazine and lever training

Each rat received at least three sessions of combined magazine and lever training during which a food pellet was delivered once each minute for 30 min (magazine training) and, in addition, each lever press produced food. The left retractable lever was extended into the chamber and 10 lever presses were reinforced; then the left lever was retracted and the right retractable lever was extended into the chamber and10 lever presses were reinforced; then the right lever was retracted and the left lever was again extended. This alternation between levers continued until the rat had pressed each lever 30 times or 30 min had passed, whichever came first. The houselight illuminated the chamber at all times during the session.

2.4. DRL—baseline training (sessions 1–25)

Rats were required to withhold responding to the extended right lever for at least 12 s in order to receive reinforcement. Responses emitted with an inter-response time (IRT) less than 12 s were not reinforced and resulted in the initiation of a new IRT. See Liao and Cheng (2005) for additional procedural details.

2.5. DRL—drug testing (sessions 26–40)

Following baseline DRL training, ketamine and vehicle injections were administered on sessions 26 and 27 using a within-subject design counter-balanced for order. Following additional baseline training, cocaine and vehicle injections were administered on sessions 39 and 40 in a similar counter-balanced manner.

2.6. DRL data analysis

Each lever press was classified by its associated inter-response time (IRT) and grouped into 1-s consecutive time bins. Lever presses with IRTs less than 2 s were defined as "burst response" and lever presses with IRTs greater than 2 s, but less than 24 s were defined as "temporally controlled" responses (see Liao and Cheng, 2005). IRT frequency distributions were determined from these temporally controlled responses. In order to obtain peak time and peak rate measures for each rat's IRT distribution, a 3-s sliding window was implemented beginning with the 3-s time bin. Peak time was defined as the mid-point of the 3-s sliding window that contained the maximum number of lever presses. Peak rate was calculated from the level of responding in the 3-s window defining peak time. This sliding-window technique for identifying peak time and peak rate was adapted from previous reports of interval timing (Liao and Cheng, 2005; Meck et al., 1984;).

2.7. Two-signal training (sessions 1–7)

Half of the rats were trained to press the left lever ("short" response) following a white-noise signal of 2 s and to press the right lever ("long" response) following a white-noise signal of 8 s. The remaining rats had this duration-lever association reversed. On each trial, one of the two signals (which differed only in duration) was randomly presented with a probability of 0.5. The noise signal was turned on for the selected duration. At the end of this interval, the signal was turned off and both levers were inserted into the box. If the rat made a correct response, a food pellet was immediately delivered; if it made the incorrect response, no food pellet was delivered. When either lever was pressed, both levers were retracted and an intertrial interval (ITI) of 5 s plus a geometrically distributed duration with a minimum of 0.1 s and a mean of 20 s was initiated. If an incorrect response had been made on the previous trial, the same signal was presented again on the next trial (correction procedure). A record was kept of the number of left and right responses following each of the two signals. Sessions lasted approximately 50 min with sufficient time allowed to complete the current trial in progress.

2.8. Seven-signal training (sessions 8–17)

The conditions of two-signal training were maintained except (a) there were no correction trials, (b) each of the two anchor durations (2 and 8 s) was presented with a probability of 0.25 on each trial, and (c) on the remaining trials, one of five

signals of intermediate duration was presented, each with equal probability. The intermediate signal durations were spaced at approximately equal logarithmic intervals between the two anchor durations used in previous training (2.52, 3.18, 4.0, 5.04 and 6.35 s). Neither the left nor the right response was followed by food in the case of these intermediate signals. A record was kept of the following characteristics of each response: (a) the subject, (b) the signal duration, (c) whether the response was left or right and (d) the response latency.

2.9. Duration bisection—drug testing (sessions 18–30)

The conditions of seven-signal training were maintained except that rats now received an intraperitoneal (i.p.) injection of 0.2 cm^3 of physiological saline, 15 mg/kg cocaine or 15 mg/kg ketamine immediately (ketamine) or 20 min (cocaine) prior to being placed in the lever boxes for the start of the session. Cocaine and ketamine injections were randomly distributed across sessions with the constraint that drug sessions would be separated by at least one saline session and that a total of three drug sessions would be obtained for both cocaine and ketamine.

2.10. Bisection data analysis

The mean proportion "long" response for each signal duration (averaged first over like-treatment sessions and then rats) was used to construct psychophysical functions for seven-signal drug testing. Responses with latencies greater than 3 s were not included in any of the data analyses because previous work showed that such responses are not well controlled by the reinforced stimulus dimension (e.g., Maricq and Church, 1983; Maricq et al., 1981). Linear regressions were conducted on the saline, cocaine and ketamine functions for individual rats by fitting the three signal durations representing the steepest portion of the psychophysical function for each of the treatment conditions (e.g., 3.18, 4.0 and 5.04 s for saline and ketamine functions, and 2.52, 3.18 and 4.0 s for cocaine functions). A point of subjective equality (PSE) was obtained by calculating the signal duration that was associated with a "long" response 50% of the time. A difference limen (DL) was also obtained from the linear regression analysis. The signal duration that was associated with a "long" response 25% of the time and the signal duration that was associated with a "long" response 75% of the time was calculated. One half of the difference between these signal durations was defined as the difference limen. A Weber fraction (WF), the DL divided by the PSE was also calculated. See Church and Deluty (1977) and Maricq and Church (1983) for additional details of these psychophysical measures obtained from the duration bisection procedure.

2.11. Drugs

Subanesthetic doses of ketamine (10 or 15 mg/kg, i.p.—Sigma, St. Louis, MO, USA) and a moderate dose of cocaine (15 mg/kg, i.p.—Sigma, St. Louis, MO, USA) were used for rats trained in both the DRL and duration bisection procedures. Doses and time of administration were selected based on the behavioral and pharmacodynamic effects of these drugs reported in the literature. Subanesthetic 10–30 mg/kg doses of ketamine exhibit a relatively short half-life (e.g., 45 min) while still producing reliable changes in locomotion and cognitive function (e.g., Imre et al., 2006; Razoux et al., 2006). In a similar manner, 10–20 mg/kg doses of cocaine produce stable changes in locomotor activity and timing behavior over the course of a 2-h session (e.g., Gulley et al., 2003; Matell et al., 2004). Solutions of cocaine and ketamine were freshly prepared prior to each injection session by dissolving the drugs in 0.9% physiological saline which served as the vehicle. Injection volumes for drugs and vehicle were 0.2 cm^3 in all cases. For the DRL procedure, all injections were administered 30 min prior to the beginning of the session, which lasted 30 min. For the duration bisection procedure, ketamine was injected immediately prior to the beginning of the session, whereas cocaine was injected 20 min prior to the beginning of the session, which lasted approximately 50 min.

3. Results

3.1. DRL: 12-s procedure

Mean IRT distributions for the DRL 12-s procedure as a function of cocaine, ketamine, and vehicle conditions are presented in Fig. 1. For these IRT distributions, the mean (±S.E.M.) peak time, standard deviation (S.D.—as defined by full-width of the normalized IRT distribution at half maximum peak-height/2) and coefficient of variation (CV—as defined by S.D./peak time) are presented for the cocaine, ketamine and vehicle treatment conditions in Table 1. Repeated measures ANOVAs indicated significant treatment effects for the cocaine vs. vehicle comparison for peak time, $F(1,5)=8.11$, $p<0.05$, and CV, $F(1,5)=74.31$, $p<0.001$, but not for S.D., $p>0.05$. No other comparisons reached significance, $p>0.05$ (see Table 1).

In addition, the total lever presses and burst responses as a function of treatment condition are presented in Table 2.

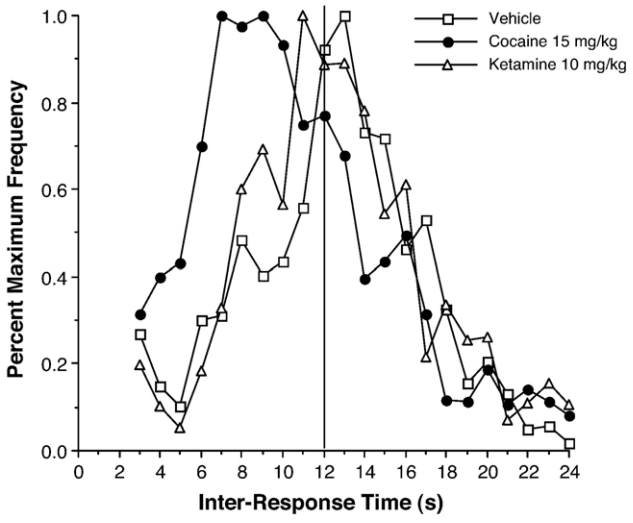

Fig. 1. Cocaine and ketamine effects in the DRL 12-s procedure. Mean percent maximum frequency of responding as a function of inter-response time during test sessions for each treatment condition. (Open squares indicate the vehicle condition; closed circles indicate the cocaine condition; open triangles indicate the ketamine condition.)

Table 1
DRL timing measures

Treatment	Peak time (s)	S.D. (s)	CV
Saline	13.58±0.69	3.0±0.65	0.22±0.05
Cocaine 15 mg/kg	9.75±1.17*	4.08±0.51	0.44±0.07*
Ketamine 10 mg/kg	12.42±0.61	3.83±0.68	0.31±0.05

Numbers=mean (±S.E.M.); S.D.=standard deviation as defined by full-width of the normalized IRT distribution at half maximum peak-height/2; CV=coefficient of variation (S.D./peak time).
* Significantly different from saline treatment ($p<0.05$).

Repeated measures ANOVAs indicated significant effects for total lever presses, $F(2,10)=14.161$, $p<0.01$, and burst responses, $F(2,10)=21.118$, $p<0.001$. Post-hoc Fisher PLSD (protected least significant difference) contrasts revealed that the total number of lever presses and burst responses were both significantly higher for the cocaine treatment condition than for the ketamine and vehicle treatment conditions, p's<0.05.

3.2. Bisection: 2- vs. 8-s procedure

Mean % "long" response functions for the 2- vs. 8-s bisection procedure are presented in Fig. 2. In addition, the mean (±S.E.M.) PSE, DL and WF bisection measures for the vehicle, cocaine and ketamine treatment conditions are presented in Table 2. Repeated measures ANOVAs indicated significant treatment effects for PSE, $F(2,18)=26.74$, $p<0.001$, and DL, $F(2,18)=10.43$, $p<0.001$, but not for WF, $F(2,18)=2.24$, $p>0.05$. Post-hoc Fisher PLSD contrasts indicated that for the PSE and DL measures the vehicle and ketamine treatment conditions were both significantly different from the cocaine treatment condition (p's<0.05), but not from each other (Table 3).

4. Discussion

The present results extend our understanding of the relationship between the dopaminergic system and the performance of time production (DRL) and time perception (bisection) tasks in rats (see Popke et al., 2000b). Systemic injections of cocaine produced a leftward shift of approximately 25% in the IRT distribution obtained from the DRL procedure and 15% in the % "long" function obtained from the bisection procedure. Conversely, there were no reliable performance effects of ketamine on either the DRL or the bisection procedure. The magnitude of the cocaine effect for the 2- vs. 8-s bisection procedure is comparable to the 20% leftward shifts observed in the tri-peak procedure for durations of 10, 30 and 90 s following systemic administration of 20 mg/kg cocaine

Table 2
DRL impulsivity measures

Treatment	Total lever presses	Burst responses
Saline	107±13.8	7.3±1.74
Cocaine 15 mg/kg	184±19.2**	34.7±6.50**
Ketamine 10 mg/kg	117±15.3	7.33±2.81

Numbers=mean (±S.E.M.).
** Significantly different from both saline and ketamine treatments ($p<0.01$).

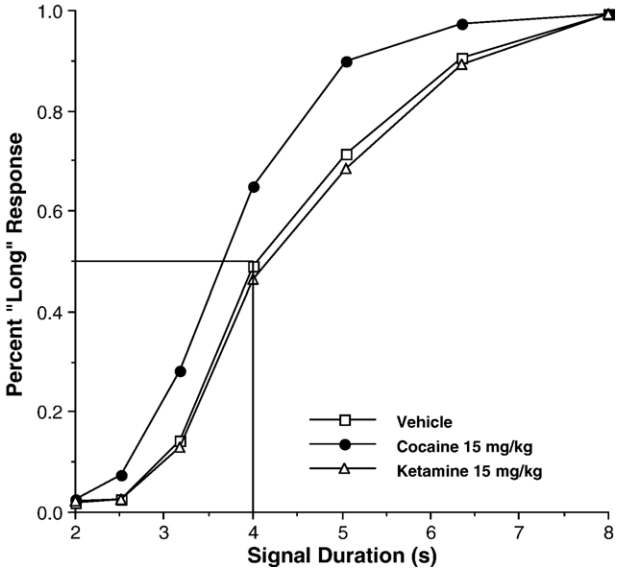

Fig. 2. Cocaine and ketamine effects in the 2- vs. 8-s bisection procedure. Mean proportion of "long" responses as a function of signal duration during the last three sessions of seven-signal drug testing for each treatment condition. (Open squares indicate the vehicle condition; closed circles indicate the cocaine condition; open triangles indicate the ketamine condition.)

(Matell et al., 2004). The size of these horizontal shifts is closer to a constant percentage than a fixed duration when comparing the different doses and durations used. In addition, the size of the drug effect would likely depend upon both dose and pharmacodynamics of the drug, which would be expected to interact with time of drug administration and session length. Taken together, these procedural differences probably account for much of the variation in the magnitude of the horizontal shifts observed for different timing procedures following drug administration (e.g., bisection, DRL, peak-interval—see Paule et al., 1999).

The cocaine-induced leftward shift observed in the PSE for the bisection procedure is consistent with an increase in clock speed (Maricq and Church, 1983; Meck, 1983). However, the true hallmark of a clock-speed effect is a left- or rightward shift that is proportional to the duration being timed. The present findings by themselves cannot resolve whether the drug effect is mediated by a faster clock because we did not test using different pairs of anchor durations (e.g., 1 vs. 4 s, 2 vs. 8 s and 4 vs. 16 s) as used by Maricq et al. (1981) and Meck (1983, 1986). However, a previous study using the "tri-peak" version of the peak-interval procedure has confirmed a proportional leftward shift in the psychophysical functions following systemic

Table 3
Duration bisection timing measures

Treatment	PSE (s)	DL (s)	WF
Saline	4.24±0.09	0.83±0.04	0.195±0.01
Cocaine 15 mg/kg	3.73±0.07**	0.64±0.02**	0.173±0.01
Ketamine 15 mg/kg	4.32±0.07	0.85±0.04	0.197±0.01

Numbers=mean (±S.E.M.); PSE=point of subjective equality; DL=difference limen; WF=Weber fraction (DL/PSE).
* Significantly different from both saline and ketamine treatments ($p<0.05$).

cocaine administration with a dose similar to that used in the present experiment (Matell et al., 2004). Therefore, a clock-speed effect is the most parsimonious explanation for our results. Moreover, the cocaine-induced leftward shifts observed in the IRT distributions are consistent with the idea that DRL performance provides an assessment of the rats' ability to estimate duration, whereas the observed increase in burst responses might be indicative of the loss of self control and heightened impulsivity (see Canon and Lippa, 1977; O'Donnell et al., 2005). Taken together, these effects are similar to previous findings using d-amphetamine or nicotine in a DRL-10 s task (e.g., Liao and Cheng, 2005; Popke et al., 2000a).

The observed behavioral dissociation with respect to the effects of cocaine and ketamine on the operation of an internal clock suggests that cocaine produces a neurochemical change that is not brought about by ketamine. There have been many studies that characterize the changes in neurotransmitter systems that take place in response to dissociative anesthetics and psychostimulants. Indeed, microdialysis studies have confirmed rapid increases in DA levels both in the dorsal and ventral striatum following systemic injections of cocaine at doses similar to those used in this study. However, the effect of ketamine on the DA system is less clear. There is little evidence to suggest that DA levels in the dorsal striatum increase by comparable amounts following subanesthetic doses of systemically administered ketamine. For example, even at ketamine doses three times those we used, dorsal striatal DA levels do not significantly change with respect to baseline. On the other hand, DA levels are readily observed to increase in the prefrontal cortex following ketamine administration (Verma and Moghaddam, 1996). Functional imaging studies have confirmed that DA levels in other brain regions, such as the ventral striatum and hippocampus, increase substantially after systemic ketamine administration (e.g., Littlewood et al., 2006). The relative specificity of ketamine with respect to its effect on limbic brain regions and prefrontal cortex are further corroborated by 2-deoxyglucose (2-DG) imaging studies (Duncan et al., 1998, 1999, 2000, 2003). These findings support the proposal that DA levels within the dorsal striatum play a fundamental role with respect to the speed of the internal clock. It should be noted, however, that a previous study reported an "overestimation of time" with a considerable disruption in timing behavior following MK-801 administration, which, like ketamine, is a non-competitive antagonist of NMDA receptors (Miller et al., 2006). Unfortunately, this study (like the present experiment) used a single temporal criterion of 12 s, thus precluding the observation of a proportional clock-speed effect. Furthermore, MK-801 is generally recognized as being a more specific NMDA antagonist than ketamine. Consequently, it is possible that we might have observed a reliable clock-speed effect had we used higher doses of ketamine due to its effect on other neurotransmitter systems (e.g., 5-HT—see Body et al., 2005).

The striatal beat-frequency (SBF) model of interval timing ascribes a mechanism for detecting event durations to medium spiny neurons within the dorsal striatum (e.g., Buhusi and Meck, 2005; MacDonald and Meck, 2004; Matell and Meck, 2000, 2004; Meck, in press-a,b). These striatal neurons have a set of functional properties that place them in an ideal position to detect behaviorally relevant patterns of afferent cortical input (e.g., Beiser and Houk, 1998). Briefly, the SBF model posits that medium spiny neurons in the dorsal striatum become entrained to fire in response to oscillating, coincident cortical inputs that become active at a trained event duration. This timing model is particularly useful insofar that the striatal neurons modeled using the SBF framework behave as they do using multiunit electrical recordings during interval-timing procedures (Matell et al., 2003). However, the exact nature of the immediate horizontal shifts in timing functions as a result of DA manipulations is undecided within the context of the SBF model. One proposal is that tonic DA levels within the striatum modulate the oscillatory frequency within the cortex through cortico-striato-thalamo-cortical feedback mechanisms (Buhusi and Meck, 2005; Matell and Meck, 2004).

Some aspects of this regulatory feedback may be mediated by the limbic system (e.g., MacDonald and Meck, 2005; Meck, 1988; Meck et al., 1986; Meck et al., 1987; Mraovitch and Calando, 1999). Indeed, the ventral striatum and amygdala have well-established roles for processing the value of reinforcement in the context of goal-directed behavior. The speed of the internal clock may also be influenced by changes in reinforcement density and/or reinforcement value (e.g., Bizo and White, 1995; MacDonald and Meck, 2005; Matell and Meck, 1999). Certain drugs, including dissociative anesthetics and psychostimulants, can change reinforcement value. For example, MK-801 has been observed to enhance responding under variable-interval schedules of reinforcement that are reinforced with intracranial brain stimulation. Ketamine behaves similarly, although its dose range for enhancing response rate is narrower than that of MK-801 (e.g., Herberg and Rose, 1989). In addition, there appears to be a synergism between the effects of cocaine and MK-801 on response enhancement, which suggests a relationship between DA and NMDA mechanisms in terms of reinforcement mechanisms (e.g., Bamford et al., 2004a,b; Dani and Zhou, 2004; Ranaldi et al., 1997).

The inability of ketamine, in contrast to cocaine, to induce a leftward shift in either of the two timing tasks used (e.g., bisection and DRL) implicates a functional significance of DA release in the dorsal striatum in terms of its role in temporal integration and the feedback control of clock speed (e.g., Buhusi and Meck, 2005; MacDonald and Meck, 2004; Matell and Meck, 2004; Meck, in press-a,b). In order to follow up on the present dissociations observed between the effects of cocaine and ketamine, future timing studies should parametrically vary the doses of DA and NMDA drugs while testing with multiple signal durations in order to determine the proportionality of the drug effects on the horizontal placement of the psychophysical functions. Such manipulations will provide the opportunity to resolve the role(s) for DA, glutamate, and NMDA in relation to timing and time perception. Moreover, genetically modified mice lacking specific DA receptors subtypes (e.g., Cagniard et al., 2006; Meck et al., submitted for publication; Miyamoto et al., 2001) and/or microinjections into specific brain regions would be preferred methods for identifying the underlying neural mechanisms of interval timing (e.g.,

MacDonald et al., submitted for publication). Indeed, given that ketamine induces changes in limbic regions of the brain, microninjections of ketamine into the hippocampus and related areas should increase the reliability and degree of separation of attention and memory decay effects from clock-speed and reinforcement-induced resetting effects (e.g., Buhusi, 2003; Buhusi and Meck, 2002, 2005, in press-a,b; Buhusi et al., 2002, 2005; Cheng et al., 2006; Matell and Meck, 1999; Meck, 2005).

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References

Bamford NS, Robinson S, Palmiter RD, Joyce JA, Moore C, Meshul CK. Dopamine modulates release from corticostriatal terminals. J Neurosci 2004a;24:9541–52.

Bamford NS, Zhang H, Schmitz Y, Wu N-P, Cepeda C, Levine MS, et al. Heterosynaptic dopamine neurotransmission selects sets of corticostriatal terminals. Neuron 2004b;42:653–63.

Beiser DG, Houk JC. Model of cortical-basal ganglionic processing: encoding the serial order of sensory events. J Neurophysiol 1998;79:3168–88.

Bizo LA, White KG. Biasing the pacemaker in the behavioral theory of timing. J Exp Anal Behav 1995;64:225–35.

Body S, Asgari K, Rickard JF, Zhang Z, Fone KCF, Bradshaw CM, et al. Effects of quipazine and *m*-chlorophenylbiguanide (*m*-CPBG) on temporal differentiation: evidence for the involvement of 5-HT2A but not 5-HT3 receptors in interval timing behavioiur. Psychopharmacology 2005;181: 289–98.

Brookes S, Rawlins JNP, Gray JA, Feldon J. DRL performance in rats with medial and lateral septal lesions. Physiol Psychol 1983;11:178–84.

Buhusi CV. Dopaminergic mechanisms of interval timing and attention. In: Meck WH, editor. Functional and neural mechanisms of interval timing. Boca-Raton, FL: CRC Press; 2003. p. 317–38.

Buhusi CV, Meck WH. Differential effects of methamphetamine and haloperidol on the control of an internal clock. Behav Neurosci 2002;116:291–7.

Buhusi CV, Meck WH. What makes us tick? Functional and neural mechanisms of interval timing. Nat Rev Neurosci 2005;6:755–65.

Buhusi, C.V., Meck, W.H. Effect of clozapine on interval timing and working memory for time in the peak-interval procedure with gaps. Behav Process, in press a.

Buhusi, C.V., Meck, W.H.. Interval timing with gaps and distractors: evaluation of the ambiguity, switch, and time-sharing hypotheses. J Exp Psychol Anim Behav Process, in press b.

Buhusi CV, Sasaki A, Meck WH. Temporal integration as a function of signal/gap intensity in rats (*Rattus norvegicus*) and pigeons (*Columba livia*). J Comp Psychol 2002;116:381–90.

Buhusi CV, Perera D, Meck WH. Memory for timing visual and auditory signals in albino and pigmented rats. J Exp Psychol Anim Behav Process 2005;31:18–30.

Cagniard B, Balsam PD, Brunner D, Zhuang X. Mice with chronically elevated dopamine exhibit enhanced motivation, but not learning, for a food reward. Neuropsychopharmacology 2006;31:1362–70.

Canon JG, Lippa AS. Use of DRL in differentiating anxiolytic and neuroleptic properties of CNS drugs. Pharmacol Biochem Behav 1977;6:591–3.

Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML. Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. Annu Rev Pharmacol Toxicol 2001;41:237–60.

Carter C. Topographic distgribution of possible glutamatergic pathways from the frontal cortex to the striatum and substnatia nigra in rats. Neuroharmacololy 1982;21:379–83.

Cheng, R.K., Liao, R.M. Dopamine receptor antagonists reverse amphetamine-induced behavioral alteration on a differential reinforcement of low-rate (DRL) operant task in the rat. Chin J Physiol. submitted for publication.

Cheng RK, Meck WH, Williams CL. α7 nicotinic acetylcholine receptors and temporal memory: synergistic effects of combining prenatal choline and nicotine on reinforcement-induced resetting of an interval clock. Learn Mem 2006;13:127–34.

Church RM. Properties of an internal clock. Ann NY Acad Sci 1984;423:566–82.

Church RM, Deluty MZ. Bisection of temporal intervals. J Exp Psychol Anim Behav Process 1977;3:216–28.

Church RM, Miller KD, Meck WH, Gibbon J. Symmetrical and asymmetrical sources of variance in temporal generalization. Anim Learn Behav 1991;19:207–14.

Dani JA, Zhou FM. Selective dopamine filter of glutamate striatal afferents. Neuron 2004;42:522–4.

Duncan GE, Leipzig JN, Mailman RB, Lieberman JA. Differential effects of clozapine and haloperidol on ketamine-induced brain metabolic activation. Brain Res 1998;812:65–75.

Duncan GE, Miyamoto S, Leipzig JN, Lieberman JA. Comparison of brain metabolic activity patterns induced by ketamine, MK-801 and amphetamine in rats: support for NMDA receptor involvement in responses to subanesthetic dose of ketamine. Brain Res 1999;843:171–83.

Duncan GE, Miyamoto S, Leipzig JN, Lieberman JA. Comparison of the effects of clozapine, risperidone, and olanzapine on ketamine-induced alterations in regional brain metabolism. J Pharmacol Exp Ther 2000; 293:8-14.

Duncan GE, Miyamoto S, Lieberman JA. Chronic administration of haloperidol and olanzapine attenuates ketamine-induced brain metabolic activation. J Pharmacol Exp Ther 2003;305:999-1005.

French E. Phencyclidine and the midbrain dopamine system: electrophysiology and behavior. Neurotoxicol Teratol 1994;16:355–62.

Gibbon J. On the form and location of the psychometric bisection function for time. J Math Psychol 1981;24:58–87.

Gibbon J, Church RM, Meck WH. Scalar timing in memory. Ann NY Acad Sci 1984;423:52–77.

Gulley JM, Hoover BR, Larson GA, Zahniser NR. Neuropsychopharmacology 2003;28:2089–101.

Hazeltine E, Helmuth LL, Ivry R. Neural mechanisms of timing. Trends Cogn Sci 1997;1:163–9.

Herberg LJ, Rose IC. The effects of MK-801 and other antagonists of NMDA-type glutamate receptors on brain-stimulation reward. Psychopharmacology 1989;99:87–90.

Hinton SC, Meck WH. Increasing the speed of an internal clock: the effects of nicotine on interval timing. Drug Dev Res 1996;38:204–11.

Hinton SC, Meck WH. The "internal clocks" of circadian and interval timing. Endeavour 1997;21:82–7.

Imre G, Fokkema DS, Den Boer JA, Ter Horst GJ. Dose–response characteristics of ketamine effect on locomotion, cognitive function and central neuronal activity. Brain Res Bull 2006;69:338–45.

Ivry RB, Hazeltine RE. Perception and production of temporal intervals across a range of durations: evidence for a common timing mechanism. J Exp Psychol Human Percept Perform 1995;21:3-18.

Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for control of behavior by reward-related stimuli. Psychopharmacology 1999;146:373–90.

Liao RM, Cheng RK. Acute effects of D-amphetamine on the differential reinforcement of low-rate (DRL) schedule behavior in the rat: comparison with selective dopamine receptor antagonists. Chin J Physiol 2005;48:41–50.

Littlewood CL, Jones N, O'neill MJ, Mitchell SN, Tricklebank M, Williams SC. Mapping the central effects of ketamine in the rat using pharmacological MRI. Psychopharmacology 2006;186:64–81.

Lustig C, Meck WH. Paying attention to time as one gets older. Psychol Sci 2001;12:478–84.

Lustig C, Meck WH. Chronic treatment with haloperidol induces working memory deficits in feedback effects of interval timing. Brain Cogn 2005;58:9-16.

MacDonald CJ, Meck WH. Systems-level integration of interval timing and reaction time. Neurosci Biobehav Rev 2004;28:747–69.

MacDonald CJ, Meck WH. Differential effects of clozapine and haloperidol on interval timing in the supraseconds range. Psychopharmacology 2005;182:232–44.
MacDonald CJ, Meck WH. Interaction of raclopride and preparatory-interval effects on simple reaction-time performance. Behav Brain Res in press.
MacDonald CJ, Cheng RK, Clore EL, Laino AM, Meck WH. Interval-timing thresholds require *de novo* protein synthesis in dorsal and ventral striatum. submitted for publication.
Maricq AV, Church RM. The differential effects of haloperidol and methamphetamine on time estimation in the rat. Psychopharmacology 1983;79:10–5.
Maricq AV, Roberts S, Church RM. Methamphetamine and time estimation. J Exp Psychol Anim Behav Process 1981;7:18–30.
Matell MS, Meck WH. Reinforcement-induced within-trial resetting of an internal clock. Behav Process 1999;45:159–71.
Matell MS, Meck WH. Neuropsychological mechanisms of interval timing behavior. BioEssays 2000;22:94-103.
Matell MS, Meck WH. Cortico-striatal circuits and interval timing: coincidence-detection of oscillatory processes. Cogn Brain Res 2004;21:139–70.
Matell MS, Meck WH, Nicolelis MAL. Interval timing and the encoding of signal duration by ensembles of cortical and striatal neurons. Behav Neurosci 2003;117:760–73.
Matell MS, King GR, Meck WH. Differential adjustment of interval timing by the chronic administration of intermittent or continuous cocaine. Behav Neurosci 2004;118:150–6.
Matell MS, Bateson M, Meck WH. Single-trials analyses demonstrate that increases in clock speed contribute to the methamphetamine-induced horizontal shifts in peak-interval timing functions. Psychopharmacology, in press.
McClure GY, McMillan DE. Effects of drugs on response duration differentiation: VI. Differential effects under differential reinforcement of low rates of responding schedules. J Pharmacol Exp Ther 1997;281:1368–80.
McGeer P, McGeer E, Scherrer U, Singh K. A glutamatergic corticostriatal path? Brain Res 1977;128:369–73.
Meck WH. Selective adjustment of the speed of internal clock and memory processes. J Exp Psychol Anim Behav Process 1983;9:171–201.
Meck WH. Affinity for the dopamine D_2 receptor predicts neuroleptic potency in decreasing the speed of an internal clock. Pharmacol Biochem Behav 1986;25:1185–9.
Meck WH. Hippocampal function is required for feedback control of an internal clock's criterion. Behav Neurosci 1988;102:54–60.
Meck WH. Modality-specific circadian rhythmicities influence mechanisms of attention and memory for interval timing. Learn Motiv 1991;22:153–79.
Meck WH. Neuropharmacology of timing and time perception. Cogn Brain Res 1996;3:227–42.
Meck WH. Neuropsychology of timing and time perception. Brain Cog 2005;58:1–8.
Meck WH. Frontal cortex lesions eliminate the clock speed effect of dopaminergic drugs on interval timing. Brain Res 2006a;in press.
Meck WH. Neuroanatomical localization of an internal clock: a functional link between mesolimbic, nigrostriatal, and mesocortical dopaminergic systems. Brain Res 2006b;in press.
Meck WH, Church RM. Abstraction of temporal attributes. J Exp Psychol Anim Behav Process 1982;8:226–43.
Meck WH, Church RM. A mode control model of counting and timing processes. J Exp Psychol Anim Behav Process 1983;9:320–34.
Meck WH, Church RM. Cholinergic modulation of the content of temporal memory. Behav Neurosci 1987a;101:457–64.
Meck WH, Church RM. Nutrients that modify the speed of internal clock and memory storage processes. Behav Neurosci 1987b;101:465–75.
Meck WH, Komeily-Zadeh FN, Church RM. Two-step acquisition: modification of an internal clock's criterion. J Exp Psychol Anim Behav Process 1984;10:297–306.
Meck WH, Church RM, Gibbon J. Temporal integration in duration and number discrimination. J Exp Psychol Anim Behav Process 1985;11:591–7.
Meck WH, Church RM, Wenk GL. Arginine vasopressin inoculates against age-related increases in sodium-dependent high affinity choline uptake and discrepancies in the content of temporal memory. Eur J Pharmacol 1986;130:327–31.
Meck WH, Church RM, Wenk GL, Olton DS. Nucleus basalis magnocellularis and medial septal area lesions differentially impair temporal memory. J Neurosci 1987;7:3505–11.
Meck WH, Sasaki A, Cevic MO, MacDonald CJ, Cheng RK, Gainetdinov RR, Caron MG. Gene-dose dependent effects of methamphetamine on interval timing in dopamine-transporter knockout mice. submitted for publication.
Melgire M, Ragot R, Samson S, Penney TB, Meck WH, Pouthas V. Auditory/visual duration bisection in patients with left or right medial-temporal lobe resection. Brain Cogn 2005;58:119–24.
Miller JP, McAuley JD, Pang KCH. Effects of the NMDA receptor antagonist MK-801 on short-interval timing in rats. Behav Neurosci 2006;120:162–72.
Miyamoto S, Mailman RB, Lieberman JA, Duncan GE. Blunted brain metabolic response to ketamine in mice lacking D(1A) dopamine receptors. Brain Res 2001;894:167–80.
Moghaddam B, Gruen R, Roth R, Bunney B, Adams R. Effects of L-glutamate on the release of striatal dopamine: in vivo dialysis and electrochemical studies. Brain Res 1990;518:55–60.
Monaghan D, Cotman C. Distribution of *N*-methyl-D-aspartate sensitive L-[3H]-glutamate binding sites in the rat brain. J. Neurosci 1985;5:2909–19.
Mraovitch S, Calando Y. Interactions between limbic, thalamo-striatal-cortical, and dentral autonomic pathways during epileptic seizure progression. J Comp Neurol 1999;411:145–61.
Niki H, Watanabe M. Prefrontal and cingulate unit activity during timing behavior in the monkey. Brain Res 1979;171:213–24.
O'Donnell JM, Marek GJ, Seiden LS. Antidepressant effects assessed using behavior maintained under a differential-reinforcement-of-low-rate (DRL) operant schedule. Neurosci Biobehav Rev 2005;29:785–98.
Paule MG, Meck WH, McMillan DE, Bateson M, Popke EJ, Chelonis JJ, et al. The use of timing behaviors in animals and humans to detect drug and/or toxicant effects. Neurotoxicol Teratol 1999;21:491–502.
Penney TB, Holder MD, Meck WH. Clonidine-induced antagonism of norepinephrine modulates the attentional processes involved in peak-interval timing. Exp Clin Psychopharmacol 1996;4:82–92.
Penney TB, Gibbon J, Meck WH. Differential effects of auditory and visual signals on clock speed and temporal memory. J Exp Psychol Hum Percept Perform 2000;26:1770–87.
Penney TB, Meck WH, Roberts SA, Gibbon J, Erlenmeyer-Kimling L. Attention mediated temporal processing deficits in subjects at high risk for schizophrenia. Brain Cogn 2005;58:109–18.
Peoples LL, Gee F, Bibi R, West MO. Phasic firing time locked to cocaine self-infusion and locomotion: dissociable firing patterns of single nucleus accumbens neurons in the rat. J Neurosci 1998;18:7588–98.
Peterson JD, Wolf ME, White FJ. Impaired DRL 30 performance during amphetamine withdrawal. Behav Brain Res 2003;143:101–8.
Popke EJ, Fogle CM, Paule MG. Ethanol potentiates nicotine's effects on DRL performance in rats. Pharmacol Biochem Behav 2000a;66:819–26.
Popke EJ, Mayorga AJ, Fogle CM, Paule MG. Comparison of drug effects on the performance of two timing tasks in rats. Pharmacol Biochem Behav 2000b;67:377–85.
Ramirez JJ, Martin C, McQuilkin ML, MacDonald KA, Valbuena M, O'Cornell JM. Bilateral entorhinal cortex lesions impair DRL performance in rats. Psychobiology 1995;23:37–44.
Rammsayer TH. Neuropharmacological evidence for different timing mechanisms in humans. Q J Exp Psychol B 1999;52:273–86.
Rammsayer TH. Effects of pharmacologically induced changes in NMDA receptor activity on human timing and sensorimotor performance. Brain Res 2006;1073–74:407–16.
Ranaldi R, Bauco P, Wise RA. Synergistic effects of cocaine and dizocilpine (MK-801) on brain stimulation reward. Brain Res 1997;760:231–7.
Razoux F, Garcia R, Léna I. Ketamine, at a dose that disrupts motor behavior and latent inhibition, enhances prefrontal cortex synaptic efficacy and glutamate release in the nucleus accumbens. Neuropsychopharmacology 2006, doi:10.1038/sj.npp.1301057.
Richards JB, Seiden LS. A quantitative interresponse-time analysis of DRL performance differentiates similar effects of the antidepressant desipramine and the novel anxiolytic gepirone. J Exp Anal Behav 1991;56:173–92.

Richards JB, Sabol KE, Seiden LS. DRL interresponse-time distributions: quantification by peak deviation analysis. J Exp Anal Behav 1993;60:361–85.

Sabol KE, Richards JB, Layton K, Seiden LS. Amphetamine analogs have differential effects on DRL 36-s schedule performance. Psychopharmacology 1995;121:57–65.

Sesack S, Pickel V. Prefrontal cortical afferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens speti and on dopamine neurons in the ventral tegmental area. J Comp Neurol 1992;320:145–60.

Sidman M. Technique for assessing the effects of drug on timing behaviors. Science 1955;122:925.

Sinden JD, Rawlins JNP, Gray JA, Jarrard LE. Selective cytotoxic lesions of the hippocampual formation and DRL performance in rats. Behav Neurosci 1986;100:320–9.

Smith GS, Schloesser R, Brodie JD, Dewey SL, Logan J, Vitkun SA, et al. Glutamate modulation of dopamine measured in vivo with positron emission tomography (PET) and ^{11}C-raclopride in normal human subjects. Neuropsychopharmacology 1998;18:18–25.

Sokolowski JD, Salamone JD. Effects of dopamine depletions in the medial prefrontal cortex on DRL performance and motor activity in the rat. Brain Res 1994;642:20–8.

Tonkiss J, Morris RGM, Rawlins JNP. Intra-ventricular infusion of the NMDA antagonist AP5 impairs performance on a non-spatial operant DRL task in the rat. Exp Brain Res 1988;73:181–8.

Van Den Broek MD, Bradshaw CM, Szabadi E. Behaviour of impulsive and non-impulsive humans in a temporal differentiation schedule of reinforcement. Pers Indiv Differ 1987;8:233–9.

Van Den Broek MD, Bradshaw CM, Szabadi E. Performance of impulsive and non-impulsive subjects on two temporal differentiation tasks. Pers Indiv Differ 1992;13:169–74.

Verma A, Moghaddam B. NMDA receptor antagonists impair prefrontal cortex function as assessed via spatial delayed alternation performance in rats: modulation by dopamine. J Neurosci 1996;16:373–9.

Wiley JL, Willmore CB. Effects of nitric oxide synthase inhibitors on timing and short-term memory in rats. Behav Pharmacol 2000;11:421–9.